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Review article

Spatial memory in Huntington's disease: A comparative review of human and animal data

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ABSTRACT

To improve the translational predictability of treatment strategies for Huntington's disease (HD), sensitive and analogous cognitive outcomes are needed across HD animal models and humans. Spatial memory measures are promising candidates because they are based on 'visual' or 'non-verbal' cognition, and are commonly tested in both animals and humans. Here, we consider the suitability of spatial memory for strengthening translational links between animals and humans in HD research and clinical trials. We describe findings of spatial memory impairments in human HD and mouse models, including which aspects of spatial memory are most affected and at which time points in disease progression. We also describe the neural systems that underlie spatial memory and link spatial memory impairments to HD neuropathology, focussing on striatal and hippocampal systems. We provide a critical analysis of the literature in terms of the suitability of spatial memory for bridging the translational gap between species. Finally, we discuss possible neural mechanisms that might explain the spatial memory impairments seen in HD, and their relevance to potential treatments.

1. Introduction

Cognitive impairment in Huntington's disease (HD) is a key symptom, for which there are no effective treatments (Bates et al., 2015). Several HD clinical trials are ongoing and potential treatments are increasingly being targeted at ameliorating the cognitive decline (Stout et al., 2017). Mouse models of HD are crucial components of preclinical testing to assess the effects of potential treatments (Menalled and Chesselet, 2002). Yet, positive results from HD mouse models have not translated to any successes in clinical trials to date (Wild and Tabrizi, 2014). There are many reasons why preclinical results in mice do not successfully translate to clinical trials in humans (Pankevich et al., 2014). One reason may be that cognitive tests used in clinical trials are misaligned with the cognitive outcomes used in the preclinical functional assessments in mouse models (Possin et al., 2016), thus minimizing the likelihood that what is observed in the mouse will be seen in the human. In HD clinical trials, cognitive outcome measures are typically selected for their sensitivity in detecting cognitive impairment in patients (Stout et al., 2017), instead of maintaining fidelity with methods used in the mouse preclinical studies. Thus, an important gap exists in clinical trial cognitive assessment methodology, which is a lack of mechanistically-driven cognitive outcome measures that are analogous on pre-clinical animal level.

Spatial memory tests are particularly suited for strengthening translational links between preclinical and clinical studies. Spatial memory can be readily tested in mice and other preclinical HD models, as well as in humans using comparable measurement approaches. Spatial memory includes the ability to learn the topographical configuration of environments, to locate objects and landmarks within environments, and to navigate from one place to another, which are functions that have ecological importance across humans and other animal species. Animal survival is reliant on effective use of spatial memories, such as knowing where one is, where food and water resources are, and how to get to safety. Humans use their spatial memory on a daily basis when making their way to work and back home, or when retrieving a mobile phone from a bag (McNamara, 2013). Across species, spatial memory relies on hippocampal and striatal networks (Chersi and Burgess, 2015), which are significantly affected in HD (Faria et al., 2016; Walker, 2007).

The purpose of this review is to evaluate the potential utility of spatial memory testing for improving translational links between animal models and humans, for the purpose of advancing clinical outcomes for people with HD. We argue that spatial memory is relevant to the cognitive phenotype of HD, and we present evidence in humans and

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animals to support this proposition. Our review starts with a description of the neuroanatomy underlying spatial memory functions, including a comparison between mouse and human anatomy. We then describe evidence, from both mice and humans, illustrating that the striatum, which is the site of the earliest and most severe pathology in HD (Walker, 2007), is an important structure within the spatial memory network. We then outline in more detail, and within the context of spatial cognition, the brain pathology and cognitive phenotype of HD. We also provide an overview of commonly used cognitive tasks in transgenic animal models of HD. Next, we show evidence from studies of HD, and from animal models of HD, which demonstrates spatial memory deficits that occur prior to the emergence of motor symptoms. This evidence is particularly important from the standpoint of measurement sensitivity, that is, the ability of spatial memory tests to detect cognitive dysfunction early in the course of HD. Finally, we critically analyse the literature in terms of the suitability of spatial memory to bridge the gap between species in HD cognitive research and in the assessment methodology of clinical trials. We also describe neural systems within which spatial memory is implemented, and their relevance to HD.

2. Neuroanatomy of spatial memory: hippocampal and striatal contributions

Like any complex cognitive domain, spatial memory in both the mouse and human is mediated by a large network involving much of the brain. Here we review two of the systems associated with spatial memory, the hippocampal and striatal systems, both of which are also affected in HD.

Within the mesial temporal lobe, the system of structures important for spatial memory includes the hippocampus and the adjacent parahippocampal, entorhinal, and perirhinal cortices. The hippocampus, which consists of the hippocampus proper (cornu Ammonis; CA1 – CA4) and the dentate gyrus, is a key and central component of the spatial memory network (Kesner and Hopkins, 2006). Its long, curved shape is present across all mammalian orders, but its internal structure and positioning within the brain differs between rodents and humans because of variations in the migration of the hippocampus during embryonic development. The human hippocampus is involved in a complete rotation during development, which leaves it in a ventral position, with CA1 in the inferior region and CA3 in the superior region (within the coronal plane). In most mammals, the hippocampus is involved in only partial hemispheric rotation during development. The rodent hippocampus, for example, is in a dorsal position, and the relation of CA1 to CA3 is thus the opposite of that found in humans (Duvernoy et al., 2013; Kier et al., 1997; see Fig. 1). Despite differences in internal organisation, the hippocampus is equally significant to spatial memory in both species (Hartley et al., 2014), as we describe below, and the organization and connections of the hippocampus with the parahippocampal, entorhinal, and perirhinal cortices, are highly conserved across brains of humans, monkeys, and rodents (Clark and Squire, 2013).

The importance of the hippocampal system to spatial memory first became apparent in the 1950s when Scoville and Milner (1957) reported the case of patient HM who became amnesic following the removal of his temporal lobes, including the hippocampi, for treatment of intractable epilepsy. HM's amnesia included a severe loss of spatial memory, which was apparent immediately following his operation and persisted for months (Scoville and Milner, 1957) and years later (Milner, 1965). By way of example, he could not find his way home alone, nor could he remember where continual-used objects were kept at home (Scoville and Milner, 1957). A subsequent key finding, in the 1970s, O'Keefe and Dostrovsky found cells that exhibit location-specific activity in the rat's hippocampus, and named them "place cells" (O'Keefe and Dostrovsky, 1971). This discovery led to the hypothesis that the hippocampus stores a cognitive map of the spatial layout of the environment (O'Keefe and Nadel, 1978). Other types of cells that support navigation, "grid cells" and "head-direction cells", were later found in the rat's entorhinal cortex, which is the main input to the hippocampus (Hafting et al., 2005; Taube, 1998). These cells form networks with place cells in the hippocampus to create a comprehensive inner global positioning system, or GPS, in the brain. Miller et al. (2015), for example, showed that individual neurons in human entorhinal cortex are activated at the same relative location across multiple paths during a virtual navigation task (Miller et al., 2015).

Lesion and stimulation studies provide another line of evidence for the importance of the hippocampus and adjacent structures in spatial memory in both rodents (Albasser et al., 2013; Kesner et al., 2015; Morris et al., 2012), and humans (Smith et al., 2011; Spiers et al., 2001; Suthana et al., 2012). Typically, lesions in the hippocampal system impair spatial memory performance on a variety of spatial memory tasks, and stimulation enhances subsequent spatial memory performance. Lesions in the perirhinal cortex alone, however, yield inconsistent results, with some studies showing impaired spatial memory performance (Liu and Bilkey, 1998a, b, c, 1999, 2001), whereas in others spatial memory was spared (Bussey et al., 2001; Glenn and Mumby, 1998; Machin et al., 2002; Ramos, 2013). Thus, damage to the perirhinal cortex may be less detrimental to spatial memory compared to lesions of the hippocampus, or to the parahippocampal and entorhinal cortices.

In humans, much of what we know about the neurocognition of memory in general, and spatial memory in particular, comes from studies on people with temporal lobe epilepsy. Early studies indicated lateralization of hippocampal involvement in memory. The right medial temporal lobe was thought to be associated with recall of *visual information and spatial relationships*, such as visuospatial recall (for example, Abrahams et al., 1997; Maguire et al., 1997; Milner, 1965; Pigott and Milner, 1993; Smith and Milner, 1981, 1989). In contrast, the left medial temporal lobe was thought to be associated with recall of *verbal material* (for example, Hermann et al., 1997; Martin et al., 2002; Saling et al., 1993). More recent findings, however, support involvement of both the right and left medial temporal lobes in spatial memory (for example, Canovas et al., 2011; Glikmann-Johnston et al., 2008; Zeidman et al., 2012).

The hippocampal system implements spatial memory by yielding a cognitive map of places and objects within the environment, independent of the actor's body orientation, termed "allocentric" or world-centred (Hartley et al., 2014). An allocentric perspective of the environment supports a flexible cognitive map, which is usable from different starting locations, or in the absence of sensory cues (Chersi and Burgess, 2015).

In contrast to the *allocentric spatial mapping* within the hippocampal system, the striatal system implements spatial processing that is *egocentric*, meaning it maps space *in relation to body location,* in conjunction with sensory cues within the environment (Chersi and Burgess, 2015; Rice et al., 2015). Rather than spatial mapping, the striatal system supports processing of the actor's location with relation to other objects in the environment, for example, learning probabilistic rules, but it is less flexible than the allocentric mapping. The striatum is the largest component of the basal ganglia, and includes the caudate nucleus, putamen, as well as the ventral striatum, which includes the nucleus accumbens, adjacent parts of the caudate, putamen, and basal forebrain. The ventral striatum receives extensive projections from the hippocampus (Chersi and Burgess, 2015). Although all mammals have a similar set of basal ganglia structures, neuroanatomical studies suggest subtle differences between species (see Fig. 2 for comparison of mouse and human striatum in HD). Relative to brain mass, the human striatum has more neurons and is significantly larger compared to rodents and non-human primates (Hardman et al., 2002; Stephan, 1979; Yin et al., 2009). The human ventral striatum has a more complex neurochemical organisation in comparison to other species (Hardman et al., 2002), which is thought to be related to the increase in size of striatal regions

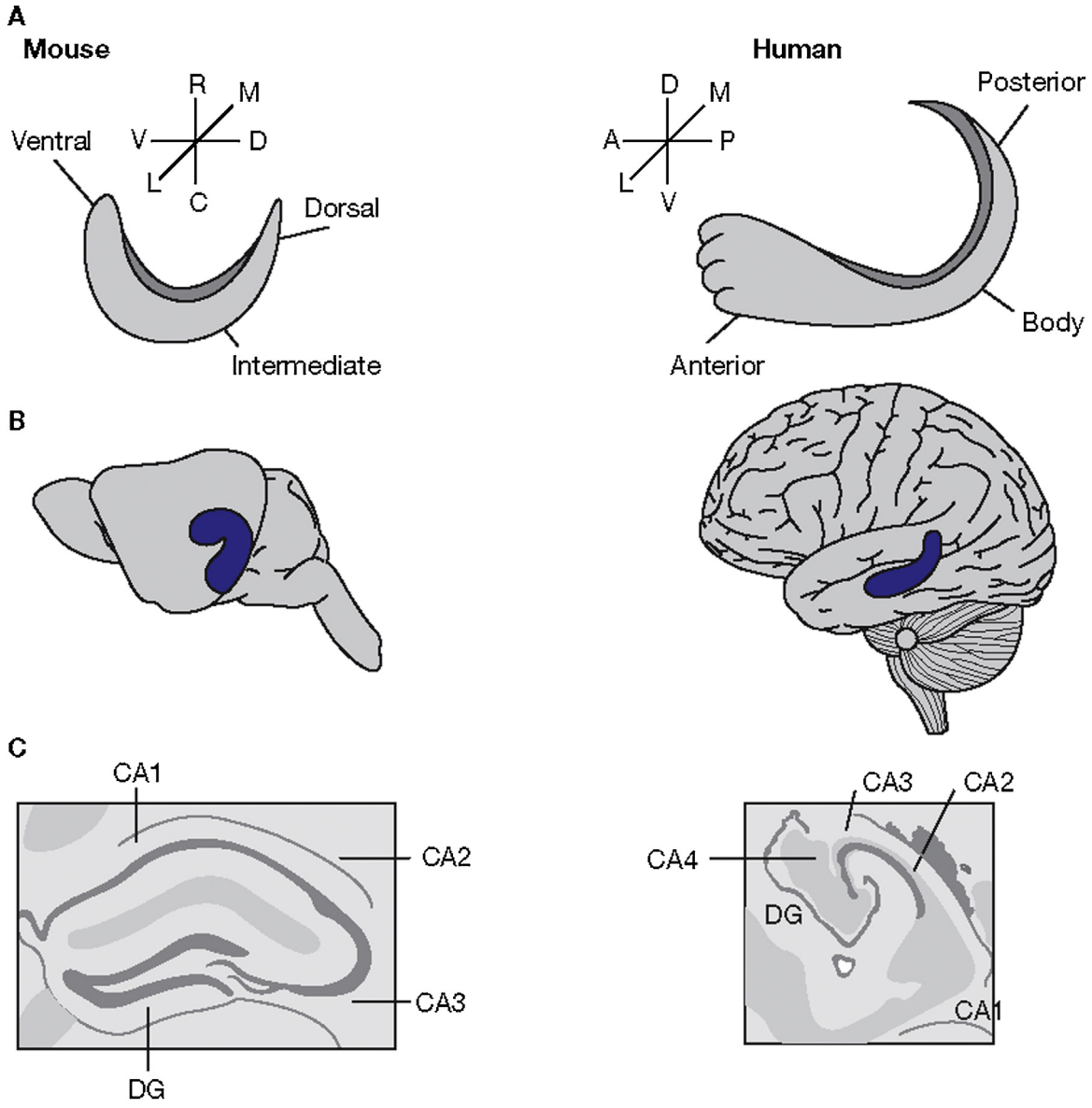

Fig. 1. Hippocampal anatomy in mouse and human (adapted from Strange et al., 2014). A. Schematic illustrations of the orientation of the hippocampal long axis in mouse and human. B. The hippocampus (blue) in brains of mice and humans. C. Drawings of Nissl cross sections of mouse and human hippocampi. Abbreviations: A, anterior; C, caudal; D, dorsal; DG, dentate gyrus; L, lateral; M, medial; P, posterior; R, rostral; V, ventral.

associated with association and limbic cortices (Holt et al., 1997).

In rodents, striatal lesions and neuropharmacological manipulations produce significant deficits across a variety of spatial learning and memory tasks (Block et al., 1993; Devan and White, 1999; Pooters et al., 2016; Sargolini et al., 2003; Sutherland and Rodriguez, 1989). De Leonbus et al. (2005) showed that for *allocentric spatial information*, the dorsal striatum (caudate nucleus and putamen) was functionally distinct from the ventral striatum (nucleus accumbens), whereas the two regions showed functional similarity in the consolidation of *egocentric spatial information*. The work by Devan and White (1999) in rodents further highlight the functional subdivisions of the dorsal striatum in relation to spatial memory. Their findings indicated that the rodent's dorsomedial striatum, in contrast to the dorsolateral striatum, mediate flexible, hippocampal-dependent spatial memory. Using a water maze, Devan and White (1999) showed that bilateral lesions to the medial caudate-putamen impaired rodents' learning of both cue (visible platform) and spatial (submerged platform) aspects of the task, and produced a preference for the cue response. In contrast, bilateral lesions of the lateral caudate-putamen did not affect acquisition of either cue or spatial components, but produced a preference for the spatial response. The subdivision of the striatum into functional gradients in connectivity and the implications for spatial cognition has been recently reviewed in both rodent and human data (Goodroe et al., 2018). In relation to spatial navigation, the authors suggested that the connections between the striatum and the hippocampus, with the former being more inflexible in terms of navigation, may enable us to make more flexible navigational responses during context-dependent spatial decision-making. In humans, striatal involvement in spatial memory has also been demonstrated using various imaging methods (Brown and Stern, 2014; Lisofsky et al., 2016; Woolley et al., 2013). Magnetic resonance imaging (MRI) has indicated increased functional connectivity between posterior hippocampus and dorsal caudate during the learning phase of the virtual water maze task (Woolley et al., 2015), which is a human analogue of the Morris water maze, a task used in rodents to test spatial memory (Morris, 1981).

The literature reviewed thus far suggests the following: (i) the hippocampal and striatal systems interact at both anatomical and functional levels across species; (ii) this interaction appears to enable

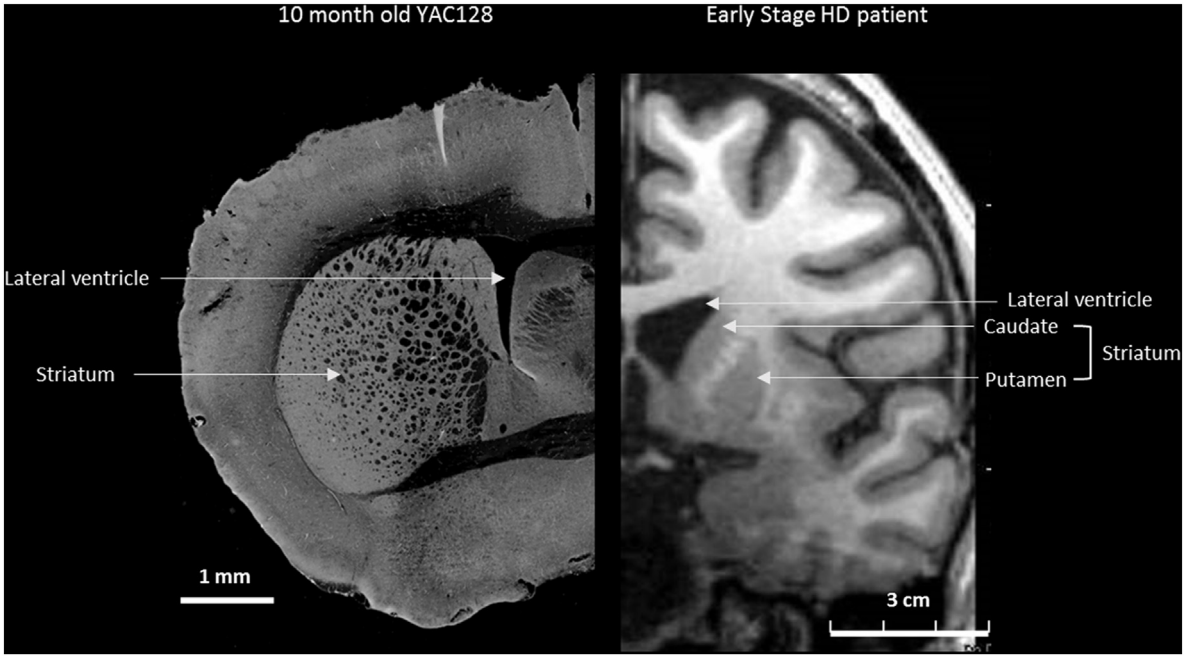

Fig. 2. Comparison of mouse and human striatum in Huntington's disease. Left is coronal view of a 10-month-old YAC128 mouse striatum from cryopreserved 30um section. It was labelled with cytochrome oxidase and images were taken at 4x and stitched together on a Keyence microscope. Right is coronal MRI section from an early-stage Huntington's disease patient showing atrophy of the caudate and putamen, and an associated increase in size of the lateral ventricle.

intact spatial memory functioning; (iii) taken together, these findings raise the possibility that spatial memory may be used as cognitive model system in conditions affecting either the hippocampus or the striatum. As we have shown earlier, spatial memory testing has been extensively used for this reason in temporal lobe epilepsy studies, in which the hippocampus is predominantly affected. In contrast, in this review, we consider spatial memory in HD because of the primary pathology within the striatum.

3. Huntington's disease: pathology and cognition

HD is an autosomal dominant neurodegenerative disorder that causes motor, cognitive, and psychiatric disturbances, eventually leading to dementia and death. Clinical diagnosis is based on the combination of unequivocal chorea and a family history or genetic confirmation of risk for HD. On average, 10–15 years before clinical diagnosis, people with the HD gene-expansion exhibit subtle cognitive decline, psychiatric symptoms, and motor signs, in what is termed the premanifest or preclinical stage (Bates et al., 2015). The cognitive impairment is a key symptom of HD, and among the most frequently reported complaint by HD patients (Stout et al., 2012; Stout et al., 2011).

HD occurs because of a pathological expansion of CAG repeat in the huntingtin (*HTT*) gene on chromosome 4, which results in a mutant huntingtin protein that contains an abnormally long polyglutamine sequence. The mutant huntingtin protein exhibits toxic properties that cause progressive dysfunction and neuronal death. GABA-ergic medium spiny neurons, which account for approximately 95% of neurons within the striatum, are particularly vulnerable to the huntingtin-induced toxicity (Bates et al., 2015; Ross et al., 2014). The neuroanatomical hallmark of HD is early and severe atrophy of the striatum and associated white matter tracts (Walker, 2007), and often, to a lesser degree, thinning of the cortical ribbon (Rosas et al., 2002). Other brain regions, such as the globus pallidus, thalamus, and hippocampus, also undergo early atrophy of a smaller magnitude to the striatum, and mostly after onset of motor symptoms (Faria et al., 2016; Jernigan et al., 1991; Younes et al., 2014). These regions have received little focus in the literature because of the field's clear emphasis on the primary pathology of HD within the striatum. Widespread brain degeneration occurs in late stages of the disease. Our knowledge about the magnitude of hippocampal degeneration in late stage HD is limited because post-mortem studies are sparse and volumetry MRI studies, understandably, include participants who can tolerate brain scanning, that is, people with early stage HD. Some indication, however, for hippocampal degeneration in late stage HD comes from one post-mortem study (Spargo et al., 1993) that found lower neuronal counts in the CA1 region of the hippocampus of nine HD cases (mean duration of disease = 9.7 years, SD = 4.5 years) compared to HIV cases and healthy controls. This difference represented a neuronal loss of 35%.

The link between brain pathology and cognitive decline in HD is not straightforward. Striatal volume loss is detectable up to 20 years before diagnosis (Dominguez et al., 2013; Tabrizi et al., 2009; Tabrizi et al., 2012; Tabrizi et al., 2011; Tabrizi et al., 2013), yet cognitive decline only becomes apparent approximately 10 years before clinical diagnosis (Harrington et al., 2012; Paulsen, 2011; Stout et al., 2011). In the far from onset period, at least 10 years before clinical diagnosis, compensatory neural processes are thought to account for the relative preservation of cognitive function in the presence of significant brain pathology, however, the precise mechanism of compensation is not yet known (Feigin et al., 2006; Georgiou-Karistianis et al., 2013; Gray et al., 2013; Papoutsi et al., 2014; Paulsen et al., 2004; Poudel et al., 2015; Scheller et al., 2013). Cognitive impairments in the preclinical and early stages of the disease are relatively subtle and selective for particular cognitive functions, but in later stages when neurodegeneration is more extensive, a wide range of cognitive domains is affected. Early cognitive symptoms typically include psychomotor slowing, executive dysfunction, and inefficiencies in attention, working memory, and emotion recognition (Paulsen, 2011; Stout et al., 2012; Stout et al., 2011).

One of the most important advances in HD research has been the generation of various mouse models that enable the study of early pathological, molecular, cellular, and cognitive abnormalities (for review see Menalled and Chesselet, 2002). In the next section we provide an overview of commonly used transgenic animal models of HD.

4. Overview of HD mouse models used to study cognition

Animal models of HD have been an invaluable resource for studying the progressive behavioural and neurological decline observed in patients, and for investigating possible neuropathological processes. Animal and cellular models are particularly valuable when they enable the study of elements of the disease process that cannot be directly evaluated in humans due to the need for more invasive approaches, or because they can be used to establish preliminary evidence of safety before 'first in human' studies. Several elements of the human disease can be usefully studied using these model systems. Naturally, models have been an essential component in the preclinical stages of drug development, where potential treatments can be tested for safety and efficacy to inform the translational potential for patients.

Essential to the consideration of using animal models in the preclinical program, is the idea that no animal model fully recapitulate the human disease. In fact, all effective models have some elements of the human disease that are demonstrated with good fidelity, but other elements have either poor fidelity to the human condition, or are absent entirely from that model. For example, the R6/2 and R6/1 mouse models of HD, both of which express the N-terminal portion of human htt, have different number of CAG repeats and phenotypic presentation. The R6/2 mice have highly expanded glutamine repeats (145–155), typically surviving for 12 to 18 weeks, and developing early progressive neurological symptoms resembling HD (at 6 to 8 weeks) (DeMarch et al., 2008; Murphy et al., 2000). Despite the presence of the phenotype, however, neurodegeneration is not detectable before 14–16 weeks, which is very late in the lifespan of the R6/2 mice (Morton et al., 2005). Thus, the R6/2 model has value for studying early deficits in synaptic physiology, cognition, and motor function (Lione et al., 1999; Morton et al., 2005), but has limited utility for studies requiring longer term cognitive or behavioural assessments, pharmacological screening, and evaluations of neuronal abnormalities. In comparison, the R6/1 mice express 116 CAG repeats, typically surviving for approximately 12 months, have later age of disease onset (at 4 to 5 months), and slower disease progression than R6/2 mice. Brain volume of R6/1 mice is significantly reduced by 18 weeks with striatal neuronal atrophy, but with no neuronal loss (Ferrante, 2009).

As a service to the field, CHDI recently released a Field Guide (http://www.chdifoundation.org/wp-content/uploads/HD_Field_Guide_040414.pdf) to help researchers select the appropriate animal model for their specific purposes. The Field Guide is an essential resource, but focuses mainly on transgenic mouse models of HD, leaving out many other useful models which are better described elsewhere (e.g., transgenic rat models and toxin-induced HD models: Chang et al., 2015; Deng et al., 2016; Fink et al., 2015; Menalled and Brunner, 2014; Stricker-Shaver et al., 2018). Furthermore, several useful large animal models are now being evaluated, including pig (Schuldenzucker et al., 2017; Yan et al., 2018), sheep (Handley et al., 2016; Pfister et al., 2018), and nonhuman primates (Li and Li, 2015; Yang et al., 2008).

Our review focuses on HD mouse models primarily because behavioural testing in large animal models have only recently begun, and so far included testing of basic cognitive functions such as visual discrimination (McBride et al., 2016; Schuldenzucker et al., 2017). To the best of our knowledge, the only study that assessed spatial memory in large animal model used a nonhuman primate (Chan et al., 2014). We begin our review with studies of spatial memory impairments in people with HD followed by studies in mouse models of HD. We then suggest potential neural mechanisms that may be responsible for the spatial memory impairments seen in HD, which may be relevant for future therapeutic interventions.

5. Spatial memory impairments in Huntington's disease

5.1. Evidence in people with HD

Studies on spatial memory in people with HD were carried out for two different purposes, first, as one of many cognitive functions interrogated in HD to create the profile of cognitive deficits, second, to specifically examine the possible role of striatal structures to egocentric spatial memory. After the identification of the CAG-expansion that causes HD in 1993 (reviewed in Wexler et al., 2016), few studies searched for cognitive tests or combinations of tests that can be used to examine the effects of candidate treatments (Stout et al., 2017; Stout et al., 2014). These tests focussed on cognitive domains largely mediated by striatal areas such as executive function and high-level attention (Maroof et al., 2011). Because little attention has been paid to cognitive domains mediated by extra-striatal structures, dysfunction in cortically-mediated cognitive domains have not been considered as primary symptoms of HD (Papoutsi et al., 2014). Recent findings from advanced neuroimaging methods, which show widespread neuropathological changes throughout the brain that occur many years before diagnosis (Ross et al., 2014) have shifted the attention to study cognitive domains related to other brain areas, outside of the basal ganglia, such as parieto-occipital and temporal cortices (for example, Johnson et al., 2015). Spatial memory is one such domain, and here we review the evidence that spatial memory deficits do occur in HD prior to motor diagnosis and are present across a variety of spatial memory components (Table 1).

To the best of our knowledge, the first study to directly examine and demonstrate spatial memory impairments in HD was published in 1971 (Potegal, 1971). In this study, HD was used as a model disease to test the hypothesis that the caudate nucleus plays a role in egocentric spatial localization. In the study, participants with HD had significant difficulties marking the original position of a target dot after changing their location. Other studies followed, examining egocentric spatial memory, with the use of variety of tasks including measures of route learning, visual discrimination, pattern recognition, visuoconstructive abilities, and visuoperception (Brouwers et al., 1984; Gomez-Tortosa et al., 1996; Lawrence et al., 1996; Lawrence et al., 2000; Mohr et al., 1991). In all of these studies, people diagnosed with HD performed significantly worse than controls. Some studies included patients with Alzheimer's disease as a comparison group to show the dissociation between striatal- and temporal-related impairments in spatial memory (in Table 1: Brandt et al., 2005; Brouwers et al., 1984; Hodges et al., 1990; Lange et al., 1995).

From 1993 onward, the availability of predictive genetic testing for HD made it possible to examine changes in spatial memory prior to the onset of motor symptoms (termed premanifest stage). Ensuing studies have evaluated spatial memory performance over defined clinical stages of HD. Generally, findings show that groups of people with premanifest HD show superior egocentric spatial memory function compared to manifest HD (Pirogovsky et al., 2015). Davis et al. (2003), however, demonstrated that manifest HD participants were impaired on *both* egocentric (hand position) and allocentric (spatial location) spatial memory. Interestingly, a later fMRI study by Voermans et al. (2004) found increased recruitment of the hippocampus during a route recognition task in premanifest and early stage manifest HD compared to healthy controls. The authors suggested that hippocampal activity increases to compensate for declining function of the caudate nucleus in order to maintain a similar level of function as healthy controls. Using the Blue Velvet Arena, a virtual water maze, which is designed to differentiate allocentric and egocentric components of spatial navigation, HD was associated with impairment in both egocentric and allocentric spatial representations (Majerova et al., 2012).

These findings have led to the recent hypothesis that extra-striatal structures might also be involved in the spatial memory deficits seen in people with HD. Initial efforts to test this hypothesis have commenced,

Table 1
Summary of studies on spatial memory in people with HD.

Citation	Participants	Spatial memory test	Components of spatial cognition	Results
Potegal, 1971	7 HD 7 PD 24 controls	A Test of Egocentric Spatial Localization: remembering the location of target dot following a head turn and a side step.	Egocentric localization	HD < controls in the side step condition only HD = PD
Brouwers et al., 1984	10 manifest HD 14 probable AD 25 controls	1 Standardized road-map test of direction sense 2 RCFT 3 Mosaic comparison test 4 Stylus Maze test	1 Route learning and recognition 2 Visuoconstructive ability 3 Visual discrimination 4 Route learning	1 Road-map test: HD < controls (on egocentric component) AD < controls 2 RCFT: HD = controls HD > AD 3 Mosaic comparison test: HD < controls AD < controls 4 Stylus Maze Test: HD = controls AD < controls
Beatty, 1989	10 manifest HD 30 controls	Fargo Map Test	Remote memory for visuospatial information and geographical knowledge	HD < controls
Hodges et al., 1990	14 manifest HD 14 probable AD 14 controls	Visual Reproduction test (copy, immediate, and delayed recall)	Memory for geometrical shapes	HD & AD < controls HD < AD on copy HD > AD on immediate and delayed recall
Mohr et al., 1991	20 manifest HD 19 controls	WAIS-R: Picture Completion, Block Design, Picture Arrangement, Digit Symbol, and Object Assembly. Embedded Figure Test, Rod and Frame Test, Mental Rotation Test, Street Map Test, Mental Reorientation Test, Extended In-Front Test	Tests were classified into three factors: overall visuospatial processing, spatial judgment, and spatial manipulation	HD < controls on overall visuospatial processing capacity and spatial manipulation HD = controls on spatial judgement
Lange et al., 1995	10 manifest HD 13 probable AD Control data pooled from published standardisation of the CANTAB	CANTAB Pattern and Spatial Recognition, Matching-To-Sample, PAL, Spatial Span, Spatial Working Memory, Tower of London, Visual discrimination/attentional set shifting	Visual learning and memory, spatial short-term memory, spatial working memory, planning, and visual discrimination	HD & AD < controls on all tests HD < AD on tests of visual learning and memory (pattern recognition, matching to sample), and spatial working memory
Lawrence et al., 1996	18 early manifest HD 18 controls	CANTAB Pattern and Spatial Recognition, Spatial Span, Spatial Working Memory, Tower of London, Visual discrimination learning/attentional set shifting	Memory for patterns and spatial locations, spatial working memory, planning, and visual discrimination	HD < controls on all tests
Gomez-Tortosa et al., 1996	35 stage 1-3 manifest HD 26 at risk asymptomatic relatives (15 gene carriers and 11 non-carriers)	Cancellation Task, Line Bisection Test, RCFT, and Hooper Visual Organization Test	Visual attention and ocular scanning, visuoconstructive and visuoperception abilities	On all tests: Manifest HD < asymptomatic relatives Manifest HD stage 1 > stage 2 > stage 3
Lawrence et al., 2000	Early-stage manifest HD Controls	CANTAB Pattern and Spatial Recognition Memory, Spatial Working Memory, PAL, Delayed Matching-To-Sample, and Visual Search/Matching-To-Sample; Spatial and Visual Working Memory, Visual Object and Space Perception Battery.	Spatial working memory, visual object and visuospatial processing	HD < controls on pattern and spatial recognition memory, delayed and simultaneous matching-to-sample, spatial (but not visual) object working memory, and pattern-location associative learning
Davis et al., 2003	12 manifest HD (10 genetically confirmed) 15 controls	Hand Position Memory Task, Spatial Location Memory Task, Judgement of Line Orientation Test, RCFT	Egocentric and allocentric spatial memory, visuoconstructive abilities	HD < controls on egocentric and allocentric memory tests
Voermans et al., 2004	12 premanifest and moderate manifest HD 18 controls	Virtual route encoding and recognition task during fMRI scanning	Route learning and recognition	Task performance: HD = controls fMRI data: HD < controls: activity in right caudate nucleus HD > controls: activity in right hippocampus
Brandt et al., 2005	110 manifest HD 143 probable AD 77 PD 147 controls (divided into young/old subgroups)	Hopkins Board	Memory for spatial locations	HD < controls For HD: recall of spatial locations < recall of item identity AD < HD < PD

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Table 1 (*continued*)

Citation	Participants	Spatial memory test	Components of spatial cognition	Results
Lineweaver et al., 2005	18 manifest HD 20 young controls 18 probable AD 20 older controls	Computerised mental rotation test	Mental rotation	HD < controls on speed, but not accuracy AD < controls on accuracy, but not speed
Majerova et al., 2012	19 manifest HD 19 controls	Blue Velvet Arena	Spatial navigation with egocentric and allocentric components	Stage I HD = controls Stages II & III HD < controls Egocentric = allocentric
Pirogovsky et al., 2015	19 mild to moderate manifest HD 30 premanifest HD 31 controls	Visual Spatial Learning Test	Memory for abstract designs, spatial location positions, and designs in positions	Premanifest HD = controls on all measure except delayed memory for designs in positions Manifest HD < premanifest HD & controls on all measures
Begeti et al., 2016	Early manifest HD Premanifest HD Controls	1 Virtual MWM 2 CANTAB PAL	1 Spatial navigation 2 Object-location memory	1 Virtual MWM: Premanifest HD = controls Manifest HD < premanifest HD & controls 2 PAL: Premanifest HD = controls Premanifest HD close to onset < premanifest HD far from onset Manifest HD < premanifest HD & controls
Labuschagne et al., 2016 (TRACK-HD study)	104 early-stage HD 119 premanifest HD 110 controls	1 Map Search 2 Computerized Mental Rotation 3 Structural brain measures	1 Visual search 2 Mental rotation	1 Map search: Early-stage and premanifest HD < controls Performance of manifest HD associated with disease burden, motor symptoms, and functional capacity. 2 Mental rotation: Early-stage HD < controls Premanifest HD = controls 3 Performance on both tasks associated with parieto-occipital and temporal volumes and cortical thickness
Possin et al., 2017	16 premanifest HD 17 controls	1 Computerized egocentric and allocentric working memory tests 2 Automated segmentation of caudate and hippocampal volumes	Egocentric and allocentric spatial memory	1 Premanifest HD < controls on egocentric test, but not allocentric test 2 Egocentric accuracy correlated with dorsolateral caudate head. Allocentric accuracy correlated with intermediate and posterior hippocampal volumes.

Abbreviations: HD: Huntington's disease; PD: Parkinson's disease; AD: Alzheimer's disease; WAIS-R: Weschler Adult Intelligence Scale – Revised; CANTAB: Cambridge Neuropsychological Test Automated Battery; PAL: Paired Associates Learning; MMSE: Mini Mental State Examination; RCFT: Rey Complex Figure Test; fMRI: functional Magnetic Resonance Imaging; UHDRS: Unified Huntington's Disease Rating Scale; TRACK-HD study: a multinational longitudinal observational study aimed at understanding the clinical manifestation and neurobiology in premanifest and early stage HD.

and focused on structures that are core to intact spatial memory function – the hippocampus and parieto-occipital cortices. For example, Begeti et al. (2016) used the virtual Morris water maze, which is a human version of the original animal task that involves virtual swimming in a circular pool in order to learn the location of a submerged hidden platform relative to external cues. These authors found spatial memory impairments on the virtual Morris water maze in manifest, but not in premanifest HD participants, and that performance levels of the manifest group were associated with disease burden scores [given by (CAG-35.5) x age]. In a study using a computerised mental rotation task, which is a visuospatial processing task, Labuschagne et al. (2016) showed that manifest, but not premanifest HD participants, performed worse compared to controls. Performance was associated with brain volume loss in occipito-parietal (pre-/cuneus, calcarine, lingual), temporal (posterior fusiform gyrus), and motor-related areas (supplementary motor area, precentral gyrus, and cerebellum). Degeneration of posterior brain areas and impairments in spatial cognition in HD have only been shown separately until recently; Labuschagne's et al. (2016) report is the first that links the two in the context of HD.

In sum, promising evidence has emerged in human HD research implicating relationships between decline in aspects of spatial cognition and atrophy in brain regions outside of the striatal region to HD. Evidence of non-striatal involvement has also been demonstrated in animal models of HD, almost exclusively in mouse models. Thus far, the only published report of spatial memory impairments in a large animal model of HD involved a longitudinal study of a transgenic HD monkey, rHD1 (Chan et al., 2014). Over the 2 years of the study, rHD1 showed progressive impairments in motor and cognitive function, including deficits in spatial memory. These deficits were associated with reduced striatal and hippocampal volumes.

5.2. Evidence in HD mouse models

Research surrounding phenotypic deficits in animal models of HD has shifted in recent years, looking beyond typical motor deficits, to exploring cognitive dysfunction, learning and memory deficits (Table 2). These deficits have extended past the typical striatal atrophy and dysfunction associated with HD and studies have begun to report pathology associated with the hippocampus as well (Bulley et al., 2012; Giralt et al., 2011; Miguez et al., 2015; Simpson et al., 2011). Hippocampal-associated behavioural tasks have been extensively tested in the transgenic HD mouse model including spatial learning tasks such as the Morris water maze and Barnes maze, spatial working memory in the radial arm maze, procedural learning tested in a reversal task in the water T-maze, recognition memory using the novel object recognition task, and delayed matching to position (DMTP) and delayed non-matching to position (DNMTP) tasks for learning and working memory (Table 2).

The YAC128 mouse model demonstrates impaired learning and memory starting at 8 months of age and progressively worsening (Van Raamsdonk et al., 2005), which has been attributed to reduced hippocampal neurogenesis in the dentate gyrus, leading to a reduced number of young neurons in the hippocampus (Simpson et al., 2011). Changes in long-term potentiation, however, are not observed in the early pre-symptomatic (6-months) hippocampus (Ghilan et al., 2014). Several molecular mechanisms have been proposed to describe the cognitive decline observed in transgenic mouse models and HD patients. These have focused on the corticostriatal pathway and suggest altered synaptic composition, deficient neurotrophic support, and transcriptional dysregulation (Giralt et al., 2012b).

The R6/2 mouse model demonstrates progressive loss of nerve growth factor levels (Zhang et al., 2013), and significant reductions of dendritic spine density and complexity in the hippocampus (Bulley et al., 2012), suggesting that the HD mutation leads to progressive pathology in the hippocampus in addition the striatum. However, the striatum does appear to be the most susceptible region of the brain early in disease progression. Using the Morris water maze, Ciamei and Morton (2009) demonstrated that young R6/2 mice (8 weeks old) performed the task with a cue-based escape strategy using shapes or cues that were placed within view of the mouse to allow for spatial recognition, which is associated with striatal function. As the disease progressed, 12-weeks-old mice shifted to a placed-based strategy, dependent on hippocampal function. Ciamei & Morton suggested that due to functional decline of the striatum the hippocampus begins to compensate for some learning based tasks (Ciamei and Morton, 2009).

It is becoming clearer that while the striatum remains the brain region most susceptible to HD-related degeneration, the hippocampus also plays an essential role, first in compensation, and then in functional deficits of learning and memory.

5.3. Potential mechanisms underlying spatial memory impairments in HD

The findings we have presented thus far have been focused on spatial memory impairments in HD from a neuroanatomical perspective, however, changes at the neuronal and neurochemical level in HD also contribute to accounts of the spatial memory deficits. Of particular relevance are changes in levels of a key neurotrophin in HD, brain-derived neurotrophic factor (BDNF). BDNF is involved in the formation of the nervous system during embryonic development, postnatal brain maturation, and regulation of synaptic transmission and neural plasticity that influence mechanisms of learning and memory (for review, see Kowianski et al., 2017; Park and Poo, 2013). In the adult brain, BDNF is highly expressed in the hippocampus, as we already showed, a brain area critical for spatial memory (Zuccato and Cattaneo, 2007). BDNF is also important for the survival of medium spiny neurons of the striatum, which receives the majority of trophic BDNF support from cortical neurons (Zuccato and Cattaneo, 2009). A loss of BDNF gene transcription is thought to be central to the progressive pathology of HD (Zuccato and Cattaneo, 2007, 2014). Reduced BDNF levels in mice models of HD have been linked to impaired learning (procedural, discrimination, and alternation learning), and to decreased levels of hippocampal long term potentiation (LTP) (Giralt et al., 2009). In knock-in mouse models of HD (Hdh^{Q92}, Hdh^{Q111}, CAG140), upregulating BDNF restored deficits in LTP (Lynch et al., 2007), and improved memory performance on a novel object recognition test (Simmons et al., 2009), thus strengthening the link between BDNF in HD neurodegeneration and spatial memory.

The spatial memory impairments in HD could also be related to disruption in the serotonergic system. Serotonin (5-HT) has long been known to be involved in learning and memory (Altman and Normile, 1988). More recently, the $5\text{-}HT_{1A}$ receptor subtype, which is highly concentrated in the hippocampus, has been specifically implicated in spatial memory (for review, see Glikmann-Johnston et al., 2015). Generally, blockade of the $5\text{-}HT_{1A}$ receptors (in knockout mouse models or by the use of antagonists) impair spatial memory, and activation (via agonists) ameliorates the blockade-induced spatial deficits, allowing normal performance. In HD, the serotonergic system is dysfunctional early in the disease. Decreased $5\text{-}HT_{1A}$ receptor binding in hippocampal and cortical regions has been found in presymptomatic and symptomatic R6/2 mice (Yohrling et al., 2002). The number of 5-HT-containing cells in the dorsal raphe nucleus, which synthesizes 5-HT, have been found to be reduced in knock-in rats, and in postmortem human tissue (Jahanshahi et al., 2013). Axons of the dorsal raphe innervate almost all regions of the central nervous system, thus affecting a great variety of behaviors, such as sleep/wake cycle, food intake, sexual behavior, emotional state, and cognitive processes, particularly learning and memory (Frazer and Hensler, 1994). Nevertheless, to date, treatments aimed at altering 5-HT levels in people with HD have not affected cognitive function. For example, the antidepressants fluoxetine (Como et al., 1997) and citalopram (Beglinger et al., 2014), both of which are selective serotonin reuptake inhibitors that increase levels of 5-HT, did not affect performance on a variety of cognitive tests. Importantly,

Table 2
Summary of studies on spatial memory in HD mouse models.

Citation	Animal model	Spatial memory paradigm	Results
Van Raamsdonk et al., 2005	YAC128 mouse model.	1 AR for motoric memory 2 OF habituation test for learning and memory 3 SWT procedural memory 4 T-S procedural learning and memory 5 Reversal phase T-S test of strategy shifting 6 PPI and habituation to acoustic startle.	1 AR: YAC128 < WT controls, progressive decline from 6-mo onward to 12-mo of age. 2 OF: YAC128 < WT in intersession habituation at 8-mo age. 3 SWT: YAC128 < WT at 8-mo of age. 4 T-S: YAC128 < WT at 8.5-mo of age. 5 Reversal swimming T-maze: YAC128 < WT at 8.5-mo of age. 6 PPI: YAC128 < WT in habituation to startle at 12-mo of age.
Nithianantharajah et al., 2008	R6/1 mouse model, males and females, raised in standard and enriched environments.	1 Y-Maze 2 NORT 3 NOLT 4 BM 5 Elevated plus maze 6 Light/dark alternation test	1 Y-Maze: R6/1 < WT in novel arm exploration beginning at 12-wks of age. 2 Novel Object Recognition: R6/1 = WT at 14-wks of age. 3 Novel Object Location: R6/1 < WT at 14-wks of age. 4 Barnes maze: R6/1 < WT finding escape 12-wks of age. Enriched R6/1 > Standard R6/1 at 12-wks of age. 5 Elevated plus maze: R6/1 = WT at 12-wks of age from both enriched and standard environments. 6 Light/dark alternation: R6/1 = WT at 12-wks of age from both enriched and standard environments.
Ciamei and Morton, 2009	R6/2 mouse model. Males only.	MWM	8-week-old R6/2 mice preferentially use a cue-based (striatal) escape strategy while 12-week-old mice use a place-based strategy (hippocampal) to escape the maze.
Giralt et al., 2011	R6/1 and R6/2 mouse model – males only.	1 NORT 2 T-SAT 3 MWM	1 NORT: Reduction in 12-wk old R6/1 in NOR-LTM compared to 4-week old. R6/2 < WT at 8-wks of age. Treated R6/2 with PKA inhibition = WT at 8-wks of age. 2 T-SAT: R6/1 < WT in LTM. 3 MWM: R6/1 < WT in time spent in quadrant.
Giralt et al., 2012a,b	HdhQ7/Q111 mouse model.	1 NORT 2 MWM	1 NORT: HdhQ7/Q111 < WT in long-term memory NORT task, but not short-term memory at 8-mo of age. 2 MWM: HdhQ7/Q111 < WT in finding target platform.
Giralt et al., 2013	R6/1 mouse model treated with a PDE10 inhibitor. Male only.	1 NORT 2 MWM	1 NORT: treated R6/1 > untreated R6/1 in long-term memory NORT task. 2 MWM: treated R6/1 > untreated R6/1 in time to platform and total platform crossings.
Rattray et al., 2013	R6/1 mouse model. Male and female.	1 T-S 2 Fear conditioning to measure memory retention and extinction.	1 T-S: male R6/1 = WT. Female R6/1 < WT deficient at 15 weeks of age. Both male and female R6/1 s developed an age-related deficit in cue reversal learning in the swimming T-maze. 2 Fear conditioning test: R6/1 s had a significantly lower fear response compared to WTs.
Southwell et al, 2013	Hu97/18, males and females.	1 NOLT 2 NORT	1 NOLT: Hu97/18 < Controls beginning at 6 mo of age. 2 NORT: Hu97/18 < Controls beginning at 9 mo of age.
Zhang et al., 2013	R6/1 mouse model infused with neural growth factor. Males and females.	Radial maze	NGF-infused R6/1 = WT following 2-week infusion of NGF. NGF-infused R6/1 < WT following 2-week wash-out of NGF.
Miguez et al., 2015	R6/1 mouse model treated with Fingolimod (FTY720). Males only.	1 NOLT 2 T-SAT	1 NOLT: FTY720 Treated R6/1 > untreated controls at 17-weeks of age. 2 T-SAT: FTY720 Treated R6/1 > untreated controls at 18-weeks of age.
Yhnell et al., 2016	HdhQ111 mouse model, males and females	1 Delayed matching to position (DMTP) 2 Delayed non-matching to position (DNMTP)	Both DMTP and DNMTP tasks revealed significant deficits in reversal learning in HdhQ111 mice.
Southwell et al., 2017	Hu128/21 mouse model, males and females.	1 T-SAT 2 NOLT 3 NORT	1 T-SAT: Hu128/21 < Controls beginning at 4 mo of age. 2 NOLT: Hu128/21 < Controls beginning at 3 mo of age. 3 NORT: Hu128/21 < Controls biegnning at 6 mo of age.
Southwell et al., 2018	Hu97/18 HD mouse. Males and females.	1 NOLT 2 NORT	1 NOLT: Hu97/18 mice treated at both 6-weeks and 6-mo of age > untreated mice when assessed at 9-mo of age. 2 NORT: Hu97/18 mice treated at 6-weeks of age > untreated controls. Hu97/18 mice treated at 6-mo of age = untreated controls.

Abbreviations: MWM: Morris water maze; NORT: novel object recognition test; NOLT: novel object location test; T-SAT: T-maze spontaneous alternation test, OF: open field; AR: accelerating rotarod; FYT720: Fingolimod; ASO: antisense oligonucleotide; SWT: simple swimming task; RM: radial maze; BT: Barnes test; T-S: T-maze swimming; PPI: prepulse inhibition; LTM: long-term memory; STM: short-term memory.

however, spatial memory tests have not been incorporated as outcome measures in any of the 5-HT-based treatment trials. In contrast, altered 5-HT receptors expression in the R6/1 mouse model has been associated with depression-related behavior (Pang et al., 2009). Separate from HD, depression has been associated with impairments in spatial navigation and abnormal hippocampal functioning (Cornwell et al., 2010), and dysregulation of the serotonergic system has been implicated as a major factor in depression (Donaldson et al., 2013). In premanifest HD, depression is the most common psychiatric symptom (Pla et al., 2014). Further explanation of the mechanisms that link

spatial memory, the serotonergic system, and depression in HD will enable us to identify more precise cognitive outcome measures that are related to HD at different levels in the testing of potential treatments.

The relationship of spatial memory with changes in BDNF levels, and with disruptions to the serotonergic system, may have important implications for potential treatments for HD. Restoration of BDNF levels appears to be a more promising method (for review see Wild and Tabrizi, 2014) than methods targeting the serotonergic system (for example, Beglinger et al., 2014), and it is our view that incorporating spatial memory as an outcome measure will prove to be beneficial for future trials.

6. Summary of the literature reviewed

The findings reviewed here provide substantial convergent evidence showing that spatial memory impairment is a cognitive symptom in HD. Since the early 1970s, findings have accumulated showing deficits in performance on a variety of spatial memory measures in people with HD. Spatial memory deficits appear to be subtle in the premanifest stage and become more pronounced as HD progresses into and through symptomatic stages. These spatial memory deficits are associated with the progressive pathology in the striatum and hippocampus. Research in HD mouse models, and in one non-human primate study, show similar findings, and strong evidence linking spatial memory impairments to HD at the neuroanatomical and neuronal levels. Specifically, mice that are genetically engineered to develop HD (R6/1, R6/2, YAC 128, Hdhq111, and HdhQ7/Q111) also develop deficits in spatial memory. Similar to the human data, striatal and hippocampal pathology, as evident by reductions in neurogenesis, dendritic spine density and complexity, are thought to be related to the spatial memory deficits. Restoration of hippocampal neurogenesis in the R6/1 mice is followed by improvements in spatial memory (for example, Miguez et al., 2015).

We have focused our review on the contributions of the striatum and hippocampus to spatial memory in HD because both structures are affected in HD, and also play key roles in spatial memory. Early and severe degeneration of the striatum is the hallmark neuropathological finding in HD. The hippocampus is also affected early in the course of the disease, but to a lesser extent than the striatum. In relation to spatial memory, the hippocampus is a key structure that facilitates allocentric learning and memory, whereas the striatum supports egocentric-based learning. The interplay between the striatum and the hippocampus has been suggested to explain the nature of spatial memory impairments seen in different stages of HD (Ciamei and Morton, 2009; Possin et al., 2017; Voermans et al., 2004). Essentially, in premanifest and early stages, when striatal degeneration is well underway, the hippocampus, which is then less affected, is thought to compensate for the lost striatal-mediated function. At this point, spatial memory is only mildly impaired, and learning and memory is achieved via hippocampal-dependent or allocentric (world-centered) frame of reference. As HD progresses, and key spatial memory structures beyond the striatum degenerate, significant spatial memory impairments are observed.

7. Critical analysis: suitability of spatial memory to bridge the gap between species in HD cognitive research and in the assessment methodology of clinical trials

The aim of this review was to analyse the utility of the spatial memory domain as a translational link between HD animal models and humans in HD cognitive research and clinical trials. We have shown on multiple and complementary levels that spatial memory has strong potential for closing the gap between animals and humans in HD cognitive research and in the efficacy assessment of HD clinical trials. First, spatial memory impairments are seen in HD and animal models of HD, across all models that were tested, including in humans, and in HD transgenic models of mice, rats, and monkeys (see Tables 1 and 2). In each of these species, spatial memory impairments are significant and occur before the emergence of motor symptoms. Second, the spatial memory impairments are evident across analogous animal-human spatial memory tests, including the rodent's MWM in Giralt et al. (2011), and the human analogue vMWM in Begeti et al. (2016) and on other tasks that assess the same spatial memory components. For example, impairments in visual pattern recognition memory have been shown in people with HD on the CANTAB pattern recognition memory (Lawrence et al., 2000), in mice on the novel object recognition test (Giralt et al., 2011), and in sheep on a two-choice object discrimination task (McBride et al., 2016). Third, all species share common brain structures and neural systems that implement spatial memory processes, namely the hippocampus and striatum, both of which are also relevant to HD neuropathology. These three lines of evidence support our assertion that testing across species can be effectively achieved by using tests within the domain of spatial memory. Alignment of cognitive tests probing similar neural systems across species has promise for improving translatability from preclinical testing through to human trials, and provides the basis for predicting efficacy in clinical trials.

What type of spatial memory tasks should be used in each stage of HD to help in the alignment of cognitive testing between people and animal models? In the premanifest period of HD when cognitive symptoms are either absent or very subtle, spatial memory tasks that combine both allocentric and egocentric components, and that engage the wider spatial memory network (Ekstrom et al., 2014), including the striatum and the hippocampus, may be appropriate. Such tasks would need to be multidimensional, potentially mimicking the spatial memory demands of everyday life, which could be achieved by the use of virtual environments. More traditional spatial memory tasks such as those used in neuropsychological assessments can be used in the manifest stages of HD because cognitive impairments, including those related to spatial cognition, are obvious at this stage and can be easily picked up. For the purpose of clinical trials, tasks of spatial navigation with aspects of object-location memory would align well with spatial memory tasks used in the preclinical testing of HD animal models.

8. Conclusion

The ability to test cognition in a comparable fashion in animals and humans is particularly important for HD and other diseases caused by trinucleotide (CAG)-repeat disorders (for example, spinocerebellar ataxias) because of the unique therapeutic opportunities. In many of the trinucleotide repeat diseases there is a significant degree of overlap in both clinical features and molecular pathology (Everett and Wood, 2004). One of the shared clinical features is disease onset. Gene carriers have no symptoms for many years until an onset at an age that is inversely correlated with the number of CAG repeats (Jones et al., 2017). In the typical adult onset HD, people appear healthy throughout childhood and early adulthood, and then gradually develop signs and symptoms of HD, leading to clinical (motor) diagnosis in middle age (Stout et al., 2011). Premanifest HD is particularly valuable in terms of finding effective therapies to slow progression. Since cognitive symptoms in premanifest HD can be subtle, sensitive and analogous cognitive measures in animal models and humans are needed to improve the translational predictability of therapeutic strategies. Our review has demonstrated that spatial memory measures have excellent potential to identify individuals beginning to show subtle signs prior to motor diagnosis, and also might be suitable for HD clinical trials as sensitive outcome measures.

For clinical trials specifically, we suggest that the implementation of cognitive testing to assess the efficacy of treatments should be approached in a strategic manner. This strategic approach should utilise a consistent and uniform cognitive assessment that spans from the preclinical program in animal models all the way to the clinical phases in humans, taking into account the translational properties of the cognitive outcome measures. This assessment methodology will ascertain

that any differences in the cognitive results between trial phases could not be attributed to differences in the cognitive measures themselves used in each phase.

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